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TOTAL SYNTHESIS OF D-*MYO*-INOSITOL 3,4,5-TRISPHOSPHATE AND 1,3,4,5-TETRAKISPHOSPHATE

J.R. Falck* and Abdelkrim Abdali
Departments of Molecular Genetics and Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas 75235 USA

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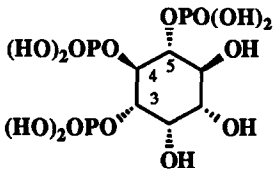
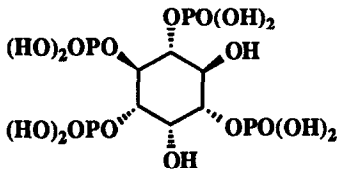
Abstract. A differentially protected chiral cyclitol was prepared from (-)-quinic acid and exploited for the total synthesis of the title *myo*-inositol polyphosphates.

The extensive investigations during recent years of the phosphatidylinositol (PI) cycle have revealed nearly two dozen inositol phosphates and related glycerylphospholipids.[1] The more recent discovery of a metabolically distinct class of 3-phosphorylated PIs associated with cellular proliferation[2] portends even greater structural diversity. While the complex interrelationship amongst many of the inositol metabolites has been established[1], the physiological role for all but a few remains obscure due, in part, to their limited availability from natural sources.[3] To help encompass the burgeoning number of new metabolites and to satisfy the urgent requirement for isomerically homogeneous standards, we report herein a significant extension of our earlier approach[4] to functionalized, chiral cyclitols from (-)-quinic acid and illustrate its versatility during total synthesis of D-*myo*-inositol 3,4,5-trisphosphate (**1**) and 1,3,4,5-tetrakisphosphate (**2**).



1

3,4,5-IP$_3$



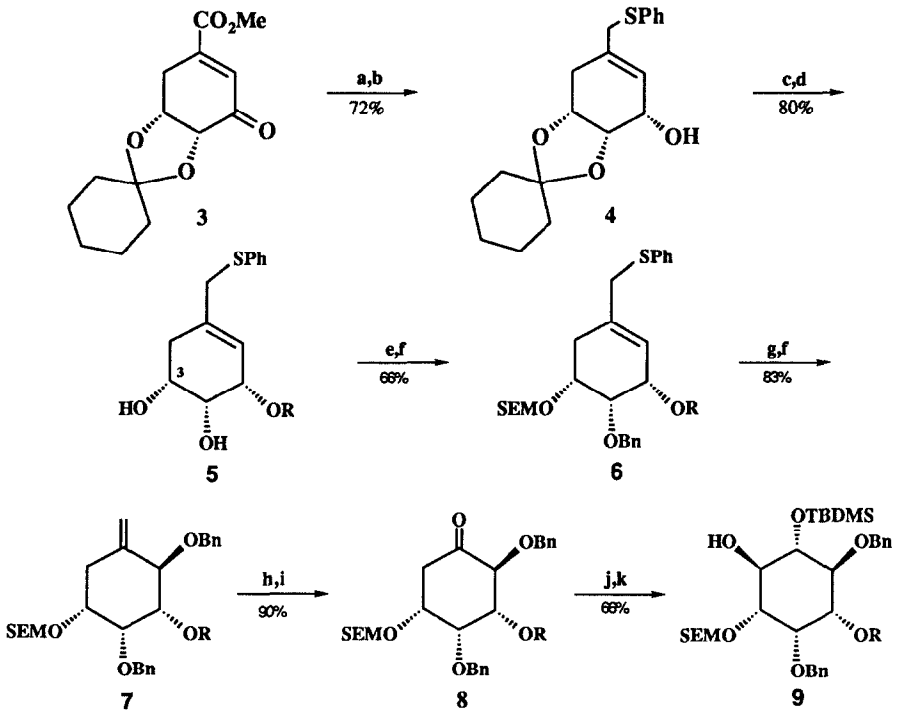
2

1,3,4,5-IP$_4$

Enone **3**, obtained in 68% yield from (-)-quinic acid[4], was converted to phenylsulfide **4**[5] (Scheme I) by concurrent diisobutylaluminum hydride (DIBAL-H) reduction of the ester and keto groups followed by selective replacement of the primary alcohol using phenyl disulfide/tributylphosphine.[6] Protection of the remaining secondary alcohol as its 3,4-dimethoxybenzyl ether and mild acidic hydrolysis of the cyclohexylidene furnished diol **5**[7], mp 85-86°C. Preferential etherification of the equatorial C(3)-alcohol (inositol numbering) via the corresponding cyclic stannylene acetal[8], prepared *in situ* from **5** and dibutyltin oxide, using equimolar amounts of 2-(trimethylsilyl)ethoxymethyl (SEM) chloride and CsF[9,10], then conventional benzylation of the axial C(2)-alcohol led to **6**. Low temperature peracid oxidation of **6** gave an ~1:1 mixture of sulfoxides that was transformed into olefin **7**, free of any α-isomer, by carefully controlled [2,3]-sigmatropic rearrangement[4] at 40°C and benzylation of the newly generated allylic alcohol. Since the 3,4-dimethoxybenzyl ether did not survive ozonolytic cleavage of the exocyclic olefin, ketone **8** was secured by an efficient two-step sequence involving OsO_4 glycolization and $Pb(OAc)_4$ oxidation. Regioselective conversion to silyl enol ether using excess *tert*-butyldimethylsilyl (TBDMS) triflate[11] and hydroboration

exclusively from the more accessible β-face was rewarded, after peracid work-up, by the fully hydroxylated and differentially protected cyclitol **9**.

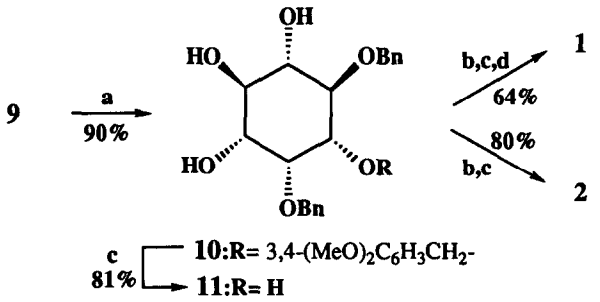
Scheme I



[a]DIBAL-H, $PhCH_3$, -78°C, 1h. [b]PhSSPh, Bu_3P, O°C, 0.5h. [c]NaH, RBr, THF, 24°C, 2h. [d]1N HCl (1.5 equiv), MeOH, 5°C, 60h. [e]*n*-Bu_2SnO, $PhCH_3$, 120°C, 4h; SEM-Cl, CsF, CH_2Cl_2, -45°C, 12h. [f]NaH, BnBr, THF, 8h. [g]*m*-CPBA, CH_2Cl_2, -78°C, 0.5h; $(EtO)_3P$ (5 equiv), MeOH, 40°C, 11d. [h]OsO_4, NMO, H_2O/acetone/*t*-BuOH (3:3:1), 0°C, 1h, then 24°C, 4h. [i]$Pb(OAc)_4$, PhH, 5°C, 20 min. [j]Et_3N (15 equiv), TBDMSOTf (6 equiv), CH_2Cl_2, 0→18°C, 4h. [k]BH_3·THF, CH_2Cl_2, 5°C, 5d; H_2O_2/NaOH; *m*-CPBA.

The utility of **9** for the synthesis of inositol polyphosphates was demonstrated (Scheme II) by hydrolysis of the SEM and silyl ethers to give triol **10**, mp 142.5 - 143.5°C. Phosphorylation (80%) according to the method[12] of Tegge and Ballou, DDQ promoted[13] cleavage of the 3,4-dimethoxybenzyl ether (89%), and catalytic hydrogenolysis (10% Pd/C, 50 psig H_2, 80% aq. EtOH) of the benzyl protecting groups gave rise to 3,4,5-IP_3 (**1**) (90%), isolated as the sodium salt. This is the first chemical synthesis of **1** which has been isolated from rat mammary tumor cells after stimulation[14] and avian erythrocytes.[15] Alternatively, treatment of **10** with DDQ afforded tetraol **11** as colorless crystals (81%), mp 144.5-145.5°C, $[\alpha]^{20}$-27°(c 0.32, EtOH); lit.[16a] mp 145.2-146.1°C, $[\alpha]^{25}$-29.2°(c 1.0, EtOH). Phosphorylation and hydrogenolysis as above gave the calcium mobilizing second messenger[17] 1,3,4,5-IP_4[16](**2**) (80%), also isolated as the sodium salt.

Scheme II



[a]1N HCl (2 equiv), MeOH, 45°C, 1.5h. [b](i-Pr)$_2$NP(OBn)$_2$, 1-H-tetrazole, CH_2Cl_2, 15°C, 1.5 h; mCPBA, -78→0°C, 1.5 h. [c]DDQ (1.5 equiv), CH_2Cl_2/H_2O (20:1), 0°C, 1.2h. [d]H_2, 10% Pd/C, 50 psig, 85% aq EtOH; NaOH.

The exploitation of **9** for the preparation of phosphatidylinositol polyphosphates and the results of pharmacologic evaluations from **1** will be reported elsewhere.

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7. ^1H NMR ($CDCl_3$, 250 MHz) of **5**: δ 2.47 (d, J~5.7 Hz, 2H), 2.67 (d, J~5.7 Hz, OH), 2.71 (d, J~9.9 Hz, OH), 3.45 (d, J~13.8 Hz, 1H), 3.50 (d, J~13.8 Hz, 1H), 3.81 - 3.95 (complex m with 2 x OCH_3 at 3.87 and 3.88, 9H), 4.42 (d, J~11.4 Hz, 1H), 4.50 (d, J~11.4 Hz, 1H), 5.50 (br s, 1H), 6.81 (s, 3H), 7.16-7.36 (m, 5H); $[\alpha]^{20}$+ 30.2°(c 1.1, CH_3CN). **7**: δ 0.02 (s, 9H), 0.84-0.96 (m, 2H), 2.42 (dd, J~4.6, 12.8 Hz, 1H), 2.63 (apparent t, J~11.6 Hz, 1H), 3.31 (dd, J~2.4, 9.4 Hz, 1H), 3.50-3.68 (complex m with OCH_3 singlet at 3.65, 6H), 3.83 (s, 3H), 4.03 (br s, 1H), 4.32 (d, J~9.4 Hz, 1H), 4.54-4.74 (m, 6H), 4.82 (d, J~11.6 Hz, 1H), 4.89 (d, J~11.6 Hz, 1H), 4.95 (br s, 1H), 5.19 (br s, 1H), 6.80-6.86 (m, 3H), 7.21-7.39 (m, 10H);

[α]^{20}- 51° (c 0.73, CH_3CN). **9**: δ 0.00 (s,9H), 0.03 (s, 3H), 0.10 (s, 3H), 0.85-1.00 (m with *t*-Bu singlet at 0.88, 11H), 2.66 (d, J~2.4 Hz, OH), 3.36 (ddd, J~9.8, 9.8, 2.4 Hz, 1H), 3.42-3.91 (complex m with 2 x OCH_3 singlets at 3.57 and 3.86, 12H), 4.06 (t, J~2.3 Hz, 1H), 4.53 (d, J~ 11 Hz, 1H), 4.58 (d, J~11 Hz, 1H), 4.69-4.99 (m, 6H), 6.74-6.78 (m, 3H), 7.22-7.42 (m, 10H); [α]^{20}- 38.3°(c 1.2, CH_3CN). **10**: δ 2.35 (d, J~8.2 Hz, OH), 2.61 (br S, OH), 2.74 (br S, OH), 3.38 (apparent t, J~9.6, 7.8 Hz, 2H), 3.48 (dd, J~2.3, 9.7 Hz, 1H), 3.70 -3.88 (complex m with 2 x OCH_3 at 3.70 and 3.88, 8H), 4.04 (br S, 1H), 4.65 (S, 2H), 4.69 (d, J~11.6 Hz, 1H), 4.76 (d, J~11.3 Hz, 1H), 5.04 (apparent t, J~11.2, 10.5 Hz, 2H), 6.80-6.89 (m, 3H), 7.28-7.36 (m, 10H); [α]^{20}-39.0° (c 0.6, CH_3CN). **1** (hexasodium salt; D_2O, 500 MHz): δ 3.63 (dd, J~2.2, 9.0 Hz, 1H), 3.87-3.92 (m, 2H), 4.00 (brt, J~7.5 Hz, 1H), 4.36 (q, J~9.0 Hz, 1H), 4.42 (t, J~2.8 Hz, 1H).

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